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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/700,737	08/15/1996	PAUL D. PONATH	LKS95-10	4692

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EXAMINER	
SCHWADRON, RONALD B	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/700,737	PONATH ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-15,18-20,23,24,27,28 and 41-56* is/are pending in the application.

4a) Of the above claim(s) *41-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-15,18-20,23,24,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The request filed on 12/12/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/700737 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 46-56 are withdrawn from consideration as drawn to nonelected inventions for essentially the same reasons that nonelected method claims 41-45 were withdrawn from consideration as elaborated in paragraphs 1-5 of the Office Action mailed 6/6/97. Regarding applicants comments about rejoinder, there are currently no allowed product claims.

3. Claims 1-9,11-15,18-20,23,24,27,28 are under consideration. Claims 1,4-9,11-15,18-20,23,24,27,28 have been amended. Claims 16,17,21,22,25,26,29-40 have been cancelled.

4. The abstract of the disclosure is objected to because it needs to be a single paragraph of less than 150 words. Correction is required. See MPEP § 608.01(b).

5. It is noted that the prior art generally refers to "chimeric antibody" as encompassing an antibody with a variable region derived from one species and a constant region derived from a different species (eg. see references , column 3, second paragraph of Ringler et al.). It is also noted that prior art generally refers to "humanized antibody" as encompassing an antibody with a human constant region, mostly human framework regions in the variable region and substituted CDRs derived from an antibody of another species (eg. see references, column 3, second paragraph of Ringler et al.). In the instant application, the term "humanized antibody" as defined in page 12 of the specification would encompass either of the aforementioned types of antibody (entire variable region grafted or CDRs grafted).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1,2,4-9,13,18,23,27,28 are rejected under 35 U.S.C. 102(e) as being anticipated by Ringler et al. (US Patent 6,551,593).

The applied reference has two common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Ringler et al. teach murine Act-1 antibody(see column 3, last two paragraphs). Ringler et al. teach chimeric or humanized (AKA CDR grafted) versions of the antibodies used in their invention (eg. Act-1)(see column 3, second and third complete paragraphs). The sequences recited in the instant claims are encompassed by the intact heavy/light chain variable regions of the Act-1 antibody or CDRs contained in the heavy/light chain variable regions of said antibody wherein said sequences are an inherent property of said antibody. The prior art refers to "chimeric antibody" as encompassing an antibody with a variable region derived from one species (generally murine) and a constant region derived from humans (eg. see references , column 3, second paragraph of Ringler et al.). The prior art generally refers to "humanized antibody" as encompassing an antibody with a human constant region, mostly human framework region in the variable region and substituted CDRs derived from an antibody of another species (generally murine) (eg. see references , column 3, second paragraph of Ringler et al.).

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-9,11-15,18-20,23,24,27,28 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. J. Immunol. 151 (11): 6482-6489 (Dec 1993)) and further in view of Ringler et al. (US Patent 6,551,593) and prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification).

Queen et al. teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen et al. teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen et al. teach that to form the humanized variable region, amino acids in the human acceptor sequence will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (column 2, Lines 35-67). Queen et al. teach that the extent of the framework region and CDR'S have been precisely defined by Kabat et al. (column 11, Lines 38-42). Queen et al. further teach that other substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (column 3, Lines 33-36). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (column 3, lines 1-31 , in particular). Queen et al. teach that typically

one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (column 13, Lines 32-40). The 21/28'CL and GM6076'CL antibody sequences were known in the art. Queen et al. teach humanized antibodies having affinity for adhesion molecules such as fibronectin and VCAM-1. Queen et al. teach humanized anti-Tac (IL-2R) (columns 45-49). Queen et al. teach that humanized antibodies have at least three potential advantages over mouse antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (column 16, lines 6-26). Queen et al. teach that humanized Igs can be more economically produced (column 68, Lines 12-14). Queen et al. do not teach humanized Act-1 (the murine derived CDRs and/or variable regions recited in the claims are derived from Act-1, a murine antibody). Lazarovits et al. teach Act-I and that the antigen recognized by Act-I is $\alpha 4\beta 7$, the receptor for fibronectin and VCAM-1. Lazarovits et al. teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (page 6487, last paragraph). Ringler et al. teach Act-1 hybridoma which would have been used to produce the nucleic acids encoding the variable regions of Act-1 wherein said sequences would have been used to produce the claimed humanized antibody. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by humanizing the Act-1 antibody as per the humanized antibodies taught by Queen et al. One of ordinary skill in the art would have been motivated to do so because Queen et al. teach their methodology can used to produce humanized antibody based on any known murine antibody and the advantages of humanized antibodies over there murine counterparts. In addition, Queen et al. disclose that humanized antibodies would be useful for therapeutic treatments, and diagnostic assays, and for purifying ligand, whilst Lazarovits et al. disclose the potential therapeutic and diagnostic value of the Act-1 antibody.

The Ringler et al. reference has been added to the previously pending rejection as teaching a source of the ACT-1 hybridoma. It is noted that Ringler et al. is an issued US Patent wherein the ACT-1 antibody is recited in the claims wherein the method was enabled for the use of said antibody via a publicly accessible deposit of said antibody (see column 3, last paragraph). The claimed invention would have been enabled at the time of filling. Regarding the various filed declarations pertaining to the ACT-1 hybridoma, said declarations do not address the Ringler et al. patent.

10. Claims 1-9,11-15,18-20,23,24,27,28 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. J. Immunol. 151 (11): 6482-6489 (Dec 1993)) and further in view prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification) as evidenced by Tiisala et al. or Mawhorter et al. or Yuan et al. or Schulz et al. or Nieto et al.

Queen et al. teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen et al. teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen et al. teach that to form the humanized variable region, amino acids in the human acceptor sequence will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (column 2, Lines 35-67, in particular). Queen et al. teach that the extent of the framework region and CDR'S have been precisely defined by Kabat et al. (Column 11, Lines 38-42, in particular). Queen et al. further teach that other substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (column 3, Lines 33-36). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (column 3, lines 1-31 , in particular). Queen et al. teach that typically one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will

most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (column 13, Lines 32-40). The 21/28'CL and GM6076'CL antibody sequences were known in the art. Queen et al. teach humanized antibodies having affinity for adhesion molecules such as fibronectin and VCAM-1. Queen et al. teach humanized anti-Tac (IL-2R) (columns 45-49). Queen et al. teach that humanized antibodies have at least three potential advantages over mouse antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (column 16, Lines 6-26). Queen et al. teach that humanized Igs can be more economically produced (column 68, Lines 12-14). Queen et al. do not teach humanized Act-1 (the murine derived CDRs and variable regions recited in the claims are derived from Act-1, a murine antibody). Lazarovits et al. teach Act-I and that the antigen recognized by Act-I is $\alpha 4\beta 7$, the receptor for fibronectin and VCAM-1. Lazarovits et al. teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (page 6487, last paragraph). Lazarovits et al. teach Act-I hybridoma which would have been used as a source of nucleic acids encoding the Act-1 heavy and light chain variable regions. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by humanizing the Act-1 antibody as per the humanized antibodies taught by Queen et al. One of ordinary skill in the art would have been motivated to do so because Queen et al. teach their methodology can used to produce humanized antibody based on any known murine antibody and the advantages of humanized antibodies over there murine counterparts. In addition, Queen et al. disclose that humanized antibodies would be useful for therapeutic treatments, and diagnostic assays, and for purifying ligand, whilst Lazarovits et al. disclose the potential therapeutic and diagnostic value of the Act-1 antibody. The cited evidentiary references deal with issues of public availability of the Act-1 hybridoma as addressed below.

Regarding the three submitted declarations about the Act-1 hybridoma, the following comments are made. The Tiisala et al. reference, page 412, first column and Mawhorter et al. reference indicate that Act-1 was obtained from Dr. Steven Shaw. While the references do not disclose that Dr. Shaw had the hybridoma, the ability to

publicly supply the antibody suggests possession of said hybridoma. Dr. Shaw is not mentioned in any of the aforementioned declarations. The Yuan et al. reference indicates that Act-1 was obtained from Dr. M.E. Hemler. While the reference does not disclose that Dr. Hemler had the hybridoma, the ability to publicly supply the antibody suggests possession of said hybridoma. Dr. Hemler is not mentioned in any of the aforementioned declarations. Schulz et al. disclose purchase of the Act-1 antibody (see page 271, second column). The commercial distribution of the Act-1 antibody would require possession of the antibody by a vendor. However, according to the Coughlin and Colvin declarations, Act-1 hybridoma was never provided to a third party manufacturer. There is no evidence of record that suggests that Leukosite, Inc actually sold the Act-1 antibody commercially. Nieto et al. disclose Act-1 antibody (see page 171, second column). While the reference does not disclose that they had the Act-1 hybridoma, the absence of a citation of a source of the antibody suggest possession of the hybridoma. The aforementioned references raise issues not addressed in the three submitted declarations.

11. Claims 1-9,11-15,18-20,23,24,27,28 are rejected under 35 US.C. 103(a) as being unpatentable over Queen et al. (U. S. Patent 5,530,101) in view of Lazarovits et al. (1993), Springer et al. (Leucocyte Typing V), Petell et al., Huston et al. (US Patent 5,258,498) and further in view prior art disclosed in the specification (the art known 21/28'CL and GM6076'CL antibody sequences as per the references cited on page 49 of the specification)

Queen et al. teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen et al. teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen et al. teach that to form the humanized variable region, amino acids in the human acceptor sequence will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (column 2, Lines 35-67). Queen et al. teach that the extent of the framework region and CDR'S have been precisely defined by Kabat et al. (Column 11, Lines 38-42, in particular). Queen et al. further teach that other substitutions are required in the

human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (column 3, Lines 33-36). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (column 3, lines 1-31). Queen et al. teach that typically one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (column 13, Lines 32-40). The 21/28'CL and GM6076'CL antibody sequences were known in the art. Queen et al. teach humanized antibodies having affinity for adhesion molecules such as fibronectin and VCAM-1. Queen et al. teach humanized anti-Tac (IL-2R) (columns 45-49). Queen et al. teach that humanized antibodies have at least three potential advantages over mouse antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be given (column 16, Lines 6-26). Queen et al. teach that humanized Igs can be more economically produced (column 68, Lines 12-14). Queen et al. do not teach humanized Act-1 (the murine derived CDRs and variable regions recited in the claims are derived from Act-1, a murine antibody). Springer et al. teach the Act-1 antibody (AKA S254 (se page 1450) and the distribution of said antibody (see page 1443, first column). Petell et al. teach that the sequence of the VH and VL encoding a known antibody can be determined by amino acid sequencing analysis of said antibody (see column 6). Huston et al. also teach that the sequence of VH and VL of a known antibody can be determined by amino acid sequencing. Huston et al. teach that:

"The 5' end portion of the mRNA can be used to produce the cDNA for subsequent sequencing or the amino acid sequence of the hypervariable and flanking framework regions can be determined by amino acid sequencing of the V regions of the H and L chains. Such sequence analysis is now conducted routinely.".

Lazarovits et al. teach Act-I and that the antigen recognized by Act-I is $\alpha 4\beta 7$, the receptor for fibronectin and VCAM-1. Lazarovits et al. teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (page 6487, last paragraph). Lazarovits et al. teach Act-I hybridoma which would have been used as a source of nucleic acids encoding the Act-1 heavy and light chain variable regions. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by humanizing the Act-1 antibody as per the humanized antibodies taught by Queen et al. using amino acid sequence information derived from sequencing the Act-1 antibody. One of ordinary skill in the art would have been motivated to do so because Queen et al. teach their methodology can used to produce humanized antibody based on any known murine antibody and the advantages of humanized antibodies over there murine counterparts. In addition, Queen et al. disclose that humanized antibodies would be useful for therapeutic treatments, and diagnostic assays, and for purifying ligand, whilst Lazarovits et al. disclose the potential therapeutic and diagnostic value of the Act-1 antibody.

Regarding applicants comments, the instant rejection does not require the Act-1 hybridoma.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Ron Schwadron whose telephone number is (571) 272-0851. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ms Christina Chan can be reached on (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1600